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Randomised, open-label, phase II trial of paclitaxel, gemcitabine and cisplatin versus gemcitabine and cisplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium

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Abstract. The purpose of the study was to evaluate the antitumor activity and the safety of paclitaxel combined with gemcitabine and cisplatin in patients affected by advanced transitional cell carcinoma of the urothelium (TCC). Eighty-five patients affected by advanced TCC and measurable disease were randomized to receive either paclitaxel at dosage of 70 mg/m^2, gemcitabine 1000 mg/m^2 and cisplatin 35 mg/m^2 on days 1 and 8 every 3 weeks (GCP) or gemcitabine 1000 mg/m^2 on days 1, 8, 15 and cisplatin 70 mg/m^2 on day 2 every 4 weeks (GC). All enrolled patients were considered evaluable for response and toxicity (intention to treat). The observed response rate was 43% for GCP and 44% for GC combination, respectively. Median time to treatment failure was 32 weeks for GCP and 26 weeks for GC and overall survival 61 vs 49 weeks, respectively (p-value not significant). Grade 3-4 neutropenia was observed in 49% of patients treated with GCP vs 35% of those treated with GC (P=0.05) and grade 3-4 thrombocytopenia was observed in 36% of GCP treated patients as compared to 21% of those treated with GC (P=0.01). Seven patients over 70 years old or with poor PS were removed from the study: 6 patients from GCP group (2 toxic deaths, 2 grade 4 myelotoxicity and 2 grade 3 asthenia) and 1 from GC group was lost to follow-up after the first cycle. The combination of paclitaxel, gemcitabine and cisplatin is effective in the treatment of TCC. However, the addition of paclitaxel to the combination of gemcitabine plus cisplatin seems to increase toxicity, therefore it seems not suitable for poor PS patients and those over 70 years old. Larger and more powered studies are needed to exactly define the role of paclitaxel in this combination.

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Introduction

Methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) or cisplatin, methotrexate, and vinblastine (CMV) have been considered as the standard treatment in patients affected by advanced transitional cell carcinoma of the urothelium (TCC) (1,2). These regimens, although effective, were associated with a high rate of toxicity, including neutropenia with its infectious complications, significant mucositis, nausea and vomiting, renal, cardiac, and neurotoxicity. Indeed, deaths due to toxicity have been reported to be as high as 3-4% even in centres experienced in the use of M-VAC (3-6).

Gemcitabine (Gemzar®; Eli-Lilly and Company, Indianapolis, IN), offers proven activity against a range of solid tumors (7-10). In particular, in metastatic urothelial cancer, gemcitabine alone yielded response rates of 23-29% with a complete response rate of 4-13%, in both previously treated and untreated patients (11). The good activity and toxicity profile of single-agent gemcitabine and its synergism with cisplatin in pre-clinical models (12) have led to the development of this combination in advanced TCC. Recently, von der Maase *et al* (13) have published a large multinational phase III trial comparing M-VAC regimen with gemcitabine plus cisplatin (GC), with a total of 405 patients accrued. The final results showed that the two regimens were similar in terms of response rate, time to progression and survival. However, the GC combination showed a better safety profile and tolerability than M-VAC. Based on these data, GC combination appeared to be a standard alternative treatment in patients affected by advanced TCC.

Paclitaxel (Taxol®), a drug that stabilizes microtubles and promotes their assembly resulting in an M-phase cell-cycle arrest (14), has been shown to be active against TTC both in preclinical as well in clinical studies (Niell HB *et al*, Proc Am Assoc Cancer Res 34: abs. 1207, 1993) (15,16). The combination of paclitaxel with cisplatin was also tested in at least 3 clinical trials: response rates of 62-72% and complete response rates of 10-34% have been reported (Murphy BA,

et al, Proc Am Soc Clin Oncol 15: abs. 617, 1996) (Dreicer R, *et al*, Proc Am Soc Clin Oncol 17: abs. 1233, 1998) (Burch PA, *et al*, Proc Am Soc Clin Oncol 18: abs. 1266, 1999). The aim of this study was to evaluate the activity of the combination of cisplatin, gemcitabine and paclitaxel in advanced TCC patients.

Materials and methods

The primary objective of this study was to define the investigator-assessed objective response rate, while the secondary objectives were to evaluate the safety and tolerability of these chemotherapy regimens. Eighty-five patients, from 11 Italian cancer centres, were randomised to receive either paclitaxel at dosage of 70 mg/m^2, gemcitabine 1000 mg/m^2 and cisplatin 35 mg/m^2 on days 1 and 8 every 3 weeks (arm A or experimental arm), or gemcitabine 1000 mg/m^2 on days 1, 8, 15 plus cisplatin 70 mg/m^2 on day 2 every 4 weeks (arm B or control arm). A maximum of 6 cycles were administered. Each patient remained in the study until disease progression was noted or until either the patient or investigator thought that it was in the patient's best interest to discontinue. The treatment was stopped in all cases of intolerable toxicity. The patients had histologically proven metastatic or unresectable transitional cell carcinoma of the urinary tract. Those who had received previous chemotherapy for advanced disease were excluded from the study. Nevertheless, patients who underwent cystectomy may have received adjuvant or neoadjuvant chemotherapy at that time but chemotherapy had to be concluded 1 year before study entry. Other eligibility criteria included written informed consent, Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and adequate bone marrow reserve, defined by a white blood count of 3,500 μl or greater, platelet count >100,000 μl and haemoglobin level >10 gm/dl. Study exclusion criteria were: inadequate liver function defined by bilirubin >1.5 mg/dl, prothrombin and partial thromboplastin time >1.5-fold normal, transaminase >3-fold normal, inadequate renal function defined by creatinine >1.5 mg/dl with calculated creatinine clearance <50 ml per min and hypercalcemia, or the diagnosis of pure squamous carcinoma or adenocarcinoma of the urothelium. Disease evaluation in all cases included tomography or magnetic resonance image (MRI) of the lesions, although accurate ultrasound was considered sufficient for hepatic metastases evaluation. Moreover, bone scan was not considered useful for evaluating bone lesions which were evaluated by X-rays or MRI. Responses were reviewed by an internal review board of radiologists and medical oncologists not participating in the study. The protocol was approved by the Ethics Committee of the Oncology Institute of Bari which was the coordinating centre of the study. With regard to dose reduction guidelines, in case of an absolute granulocyte count of 1,000-1,500x10^6 l and or platelet count between 110,000-75,000 ml on treatment day, patients had a 50% dose reduction of gemcitabine and paclitaxel with full dose of cisplatin. In case of lower values, treatment was delayed until recovery. In addition, grade 3-4 WHO non-haematological toxicity other than nausea, vomiting or alopecia required a 25% dose reduction of each drug as well as complete recovery before therapy restoration. After the completion of two treatment courses, all patients underwent re-evaluation, including a repeat of all previously abnormal radiological studies. Patients were assigned a response category using standard World Health Organization (WHO) definitions. A complete response required the complete resolution of all clinical evidence of a tumor, as determined by two observations not <4 weeks apart. A partial response required a decrease ≥50% in the size of measurable lesions, as determined by the sum of the greatest tumor dimensions, with no new lesions appearing. Stable disease was defined as a decrease <50% or an increase <25% in tumor measurements, with no new lesions appearing. Progressive disease occurred when measurable lesions increased in size by >25%, evaluable lesions worsened or new lesions appeared.

Table I. Patient characteristics.

Demographics	GCP	GC
Entered/evaluable	42	43
Early drop out:	6	1
Grade 4 myelotoxicity	4	-
Grade 3 asthenia	2	-
Lost to follow up	-	1
Male/female	40/2	41/2
Median age (range)	69 (48-76)	68 (49-76)
Performance status:		
0	18	19
1	16	18
2	8	6
Prior treatment:		
(Neo)/adjuvant	4	5
Primary tumor site:		
Bladder	41	40
Renal pelvis	1	3
Metastatic sites:		
Locally advanced only	10	14
Nodal/soft tissue only	9	10
Liver	8	6
Bone + nodal	7	5
Lung	8	7
Peritoneal carcinomatosis	-	1

Statistical considerations. The primary endpoint of this study was to evaluate the response rate and safety of the combination of paclitaxel, gemcitabine and cisplatin. We chosen a phase II randomised design in order to avoid selection bias. Therefore, the second arm or control arm constituted the combination of gemcitabine plus cisplatin was considered the standard arm. The two arms proceeded independently and a sequential 2-step statistical test of Gehan to define the number of patients required to detect the activity of the treatment could be applied

Table II. Response rates.

	GCP	GC
No evaluable patients	42	43
Complete response	5 (12%)	3 (7%)
Partial response	13 (31%)	16 (37%)
Stable disease	12 (29%)	10 (23%)
Progressive disease	12 (29%)	14 (33%)
Overall response rate	43%	44%
95% CI	23-63	28-60
Median time to progression	32 weeks	26 weeks
Median survival	61 weeks	49 weeks

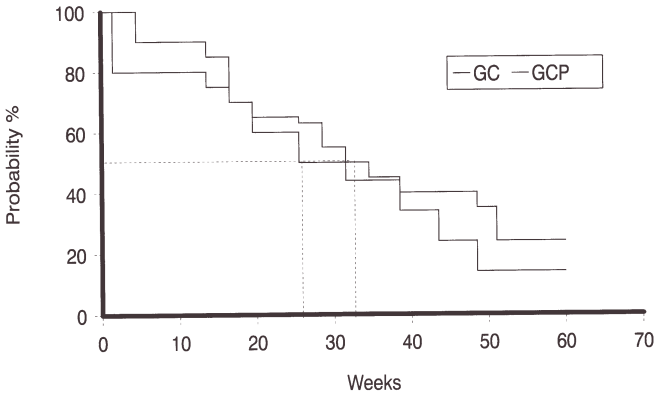

Figure 1. GCP vs GC in bladder cancer: a phase II randomised study: time to treatment failure.

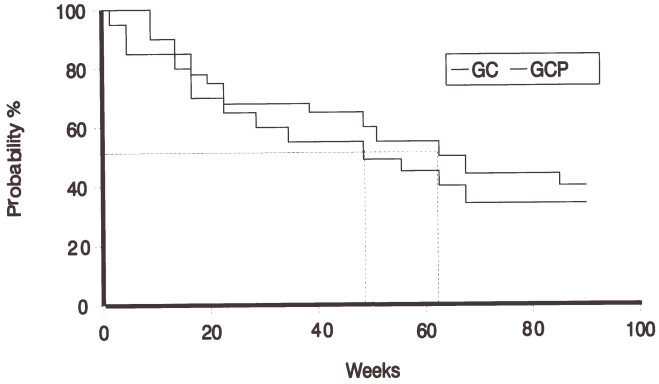

Figure 2. GCP vs GC in bladder cancer: a phase II randomised study: overall survival.

(17). After the first 16 patients were randomised to the experimental arm, at least 7 responses were required to proceed to the next accrual target of 43 cases to ensure with 95% confidence that a true response was at least 35%. We used the Kaplan-Meier method to analyse time to progression and overall survival. Confidence intervals (CI) of the response rates were calculated using the method described by Simon (18). Because of the scant number of patients in each arm of the study, no direct comparisons in activity, but only single arm evaluation of tolerability is allowed.

Results

Eighty-five patients entered on this phase II randomised trial from December 1999 to January 2002 by 11 Italian centres. The characteristics of patients who received at least one cycle of chemotherapy are compared in Table I. There were no significant differences in age, gender, performance status, stage and metastatic site involved between the two groups. The responses of patients who were treated with each of the two regimens are illustrated in Table II. Of 42 patients treated with GCP, 4 patients discontinued treatment after the first cycle because of grade 4 life-threatening myelotoxicity which caused 2 toxic deaths due to neutropenic sepsis and 2 patients discontinued after the second cycle due to grade 3 asthenia. On the other hand, no patient suffered from life-threatening toxicity in the GC arm but 1 patient was lost to follow up after the first cycle. If we consider all randomised patients as evaluable for response and toxicity on an intent to treat basis, 5 complete responses plus 13 partial responses were recorded in GCP arm for an overall response rate of 43%, whereas 3 complete responses plus 16 partial responses for an overall response rate of 44% for GC arm were observed, respectively (P= N.S.). The 95% confidence intervals for the response rate were 23-63% in GCP arm and 28-60% in GC arm. An additional 12 patients for GCP arm (29%) and 10 patients for GC arm (23%) had stable disease and 12 (29%) and 14 (33%) patients progressed respectively. The median time to treatment failure was 32 (range 2-40+) and 26 (range 2-43+) weeks, and median survival was 61 (range 2-85) and 49 (range 2-72) weeks for GCP and GC treated patients, respectively (Figs. 1 and 2).

Toxicity. The three-drug regimen (GCP) was more myelotoxic than the two-drug regimen (GC) as illustrated in Table III. Grade 3 and 4 leukopenia were less frequent with the two-drug combination (35 vs 49% P=0.053) and also thrombocytopenia was significantly less frequent with the two-drug combination (21 vs 36% P=0.018). No significant differences were observed in G 3-4 anaemia (24 vs 19.6% P=0.73). The non-haematological toxicities are illustrated in Table IV. Overall, considering all toxicity grades, the GC regimen was less toxic as compared to GCP regimen with regard to infection (5 vs 9%), asthenia (2 vs 15%), mucositis (2 vs 12%), diarrhoea (0 vs 7%), neurotoxicity (7 vs 17%), renal (10 vs. 12%). No differences were observed in the incidence of nausea and vomiting (47 vs 40% respectively) and ototoxicity (5 vs 2% respectively). There were two treatment related deaths in GCP arm which occurred after the first cycle in 2 patients over 70 and with poor PS, both due to sepsis. Haematological growth factors (G-CSF) were used in 23 patients of GCP arm (55%) and in 11 (26%) patients of GC arm in order to overcome haematological toxicity. However, most of G-CSF were given prophylactically to patients with an older age or poor PS in order to avert grade IV neutropenia. This happened particularly after we recorded the two toxic deaths.

Table III. Hematological toxicity.

Toxicity	GCP (107 cycles)		GC (121 cycles)	
Grade	G 3	G 4	G 3	G 4
Leukopenia	20%	29%	18%	17%
Thrombocytopenia	15%	21%	7%	14%
Anemia	9%	11%	10%	14%

Table IV. Non-hematological toxicity.

Toxicity	GCP (42 patients)		GC (43 patients)	
Grade (%)	1-2	3-4	1-2	3-4
Infection	1 (2)	3 (7)	2 (5)	-
Nausea/vomiting	10 (23)	7 (17)	9 (21)	11 (26)
Asthenia	4 (10)	2 (5)	1 (2)	-
Mucositis	2 (5)	3 (7)	1 (2)	-
Diarrhea	3 (7)	-	-	-
Neurotoxicity	5 (12)	2 (5)	3 (7)	-
Renal	3 (7)	2 (5)	2 (5)	2 (5)
Ototoxicity	-	1 (2)	-	2 (5)

Discussion

For more than a decade the M-VAC regimen has been the gold standard chemotherapy in bladder cancer, albeit that the toxicity associated with this therapy hampered its use in many of the typical elderly patients with metastatic disease. More recently, the randomised trial comparing the combination of gemcitabine, cisplatin (GC) with M-VAC in 405 patients, has showed similar efficacy for the two regimens with respect to response, time to progression, and overall survival, but with much lower toxicity associated to GC. Based on this superior risk-benefit ratio, the two-drug combination GC became the new standard of care in patients with locally advanced and metastatic urothelial cancer. However, the development of more effective regimens for patients with metastatic bladder cancer remains a priority. The Spanish Oncology Genitourinary Group conducted a phase I/II trial combining gemcitabine, cisplatin and paclitaxel (19). Fifteen patients were entered at 4 different dose levels in the phase I part of the study. Dose-limiting toxicity was grade 2 and 3 asthenia at dose level 4. The recommended doses for the phase II part of the study were gemcitabine, 1000 mg/m^2, on days 1 and 8; paclitaxel, 80 mg/m^2 as a 3 h infusion, on days 1 and 8; and cisplatin, 70 mg/m^2, on day 1, every 21 days. An additional 46 patients were entered in the phase II portion, resulting in a total of 49 patients at the specific dose level (3 patients from the phase I part). A total of 58 patients were evaluable for response, with an overall response rate of 78% and a CR rate of 28%. Responses were observed at all dose levels and in all disease sites. The median survival for the phase I portion of the study was 24 months, subsequently reduced to 15.8 months when enough follow-up was available for the entire group of the patients (20). However, this regimen was very toxic. In fact, full dose was possible only in 15/46 patients (32.6%), 9 patients were removed from the study for toxicity (1 death due to neutropenic sepsis, 1 because of haematological toxicity, 3 because of renal toxicity and 4 because of non-haematological toxicity). Moreover, G-CSF were given to 18 patients in 42 cycles. Another triple combination was reported by Bajorin *et al* (21) who combined ifosfamide, 1.5 g/m^2 daily, on days 1-3; paclitaxel, 200 mg/m^2 in 3 h on day 1; and cisplatin, 70 mg/m^2 on day 1 with granulocyte colony stimulating factors administered during each 28-day treatment cycles. A total of 44 patients were evaluable for response, with an overall response rate of 68% and a CR rate of 23%. The median survival was 20 months. Toxicity seemed to be independent of whether the treatment was recycled at 3 or 4 weeks. The most important grade toxicity was myelo-suppression. Seven patients (16%) had neutropenic fever. Non-haematological toxicities included grade 3 renal insufficiency (11%), and grade 3 neuropathy occurred in 9% of the patients. In a study by Hussain *et al* (22), 49 patients received gemcitabine 800 mg/m^2 on day 1 and 8, paclitaxel 200 mg/m^2 in 3 h on day 1 and carboplatin AUC 5 on day 1 every 21 days. Prior chemotherapy for metastatic disease was not allowed. The overall response rate for 47 evaluable patients was 68% with a CR rate of 32%. Responses were observed in all sites and within 15 of 22 patients with visceral metastases. The median survival was 14.7 months. The major toxicities were grade 3-4 neutropenia and grade 3-4 thrombocytopenia in 73 and 43% of patients, respectively. There were no toxicity related deaths.

In this study we have treated 42 patients with a triple combination (gemcitabine, paclitaxel and cisplatin) and 43 patients with a doublet of gemcitabine/cisplatin in randomised fashion. The phase II randomised design of the study was chosen in order to avoid selection bias that often influence results of phase II studies. However, the type of study chosen and the number of patients in each treatment arm do not allow to draw any definitive conclusion regarding responses and survival. On the other and, this type of study is planned to give information of feasibility of a new regimen with particular regard to safety. In this regard, the response and toxicity data of the GC arm are comparable to those reported in a number of studies in literature, therefore we can assume, because of the randomised phase II trial, that cases also in the GCP arm were not a particularly selected patient group. Noteworthy in this study is the outcome of patients treated with the triple combination. This combination was derived from that used by Bellmunt (19) and modified splitting cisplatin in 2 doses of 35 mg/m^2 given on days 1 and 8 instead of the 70 mg/m^2 on day 1 of the original Bellmunt schedule. Moreover, paclitaxel dosage was slightly decreased to 70 mg/m^2 on days 1 and 8 (instead of 80 mg/m^2) in the hope of further reduction in the toxicity of the Spanish regimen, however, without success. In fact, in the Bellmunt study, a full dose of drugs was administered only in 15/46 patients in the phase II part of the study (32.6%) and 9 patients were removed from the study for toxicity, moreover G-CSF was given to 18 patients and 42 cycles. In our study, despite the schedule changes, grade 3-4 leukopenia was

observed in 49% of cycles, grade 3-4 thrombocytopenia in 36% of cycles and 2 patients although older than 70 and with poor PS died of toxicity. Moreover, another significant nonhematological toxicity (already reported by Bellmunt) was asthenia which was observed in 6 patients and caused refusal to continue in 2 patients. The conclusion is that the triple regimens are more toxic than the doublets.

With regard to the activity of this regimen, our data does not support the enthusiastic responses of Bellmunt *et al*. In fact, we observed 3 complete and 15 partial responses among 42 treated patients for an overall response rate of 43% which is significantly lower than that reported by Bellmunt *et al*.

The possible reasons for this response default may be the older median age of our patients (69 vs 66) and other pre-treatment factors (i.e. patient selection) which may have an impact on the outcome in terms of response and survival.

In conclusion, the combination of gemcitabine, paclitaxel and cisplatin in this phase II randomised study did not achieve results superior to those reported in literature in a number of studies with a gemcitabine/cisplatin comprising doublet. On the other hand, the toxicity was relevant confirming the previous reports with similar combinations. However, only the results of the large randomised phase III trial still ongoing by EORTC, comparing GCP vs GC in a large number of patients, will definitively state if the addition of paclitaxel to gemcitabine/platinum will really improve the response and survival of these patients, or only add toxicity, abolishing any potential advantage over M-VAC.

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